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REMARKS

Claims 1, 3-5, and 11-12 have been amended. Claims 6-8 and 15-17 have been cancelled. Claims 18 has been added. No new matter has been added. Claims 1-17 are pending in the application. Applicant respectfully requests reconsideration of the application in light of the amendments and the following remarks.

REJECTIONS UNDER 35 U.S.C. 112

Rejections Under 35 U.S.C. 112, Second Paragraph

Claims 1-17 are rejected under 35 U.S.C. 112 Second Paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

It appears that the use of the term "derivative" in claim, among others, triggered the rejection under the 35 U.S.C. 112, Second Paragraph. For this reason the term "derivative" has been deleted from the rejected claims. Since the offending term is no longer in the claims, Applicant respectfully requests reconsideration of claims 1-17 and withdrawal of the rejection.

35 U.S.C 112, First Paragraph

Claims 1-17 are rejected under 35 U.S.C. 112, First Paragraph for the reason that the specification while being enabling for certain methods of treatment does not reasonably provide enablement for all the method of use such as oncoses, uncontrolled proliferation, infective diseases, immunomodulatory action as claimed.

Claims 1 and 2 are directed to novel disorazole compounds represented by the generic formula I described in claim 1. Claims 1 and 2 are not directed to methods of treatment of any disease state. Surprisingly, claims 1 and 2 are rejected on the basis that they are not reasonably enabled by the specification for treating oncoses, uncontrolled proliferation, infective diseases or immunomodulatory action. This rejection is improper in view of the fact that claims 1 and 2 are

not even method of use claims. Applicant, therefore, respectfully requests withdrawal of this groundless rejection of claims 1 and 2.

Claim 3 is directed to a pharmaceutical composition comprising a disorazole compound of the general formula Ia (see claim 3 for more details of general formula Ia). However, it is being rejected under 35 U.S.C 112, First Paragraph for not being reasonably enabled by the specification for treating oncoses, uncontrolled proliferation, infective diseases or immunomodulatory action. The reason for this rejection of claim 3 under 35 U.S.C 112, First Paragraph does not make any sense in view of the fact that claim 3 does not recite method of treatment; it recites a pharmaceutical composition comprising a compound of the general *formula Ia.* The reason given does not justify rejection of claim 3 under 35 U.S.C 112, First Paragraph. Therefore, Applicant respectfully requests withdrawal of this groundless rejection of claim 3.

Claim 4 is directed to a method for the treatment of oncoses comprising administering the compound of generic *formula Ia* to an individual in need of such treatment alone or in combination with a cytotoxic substance and/or an inhibitor of signal transduction. This claim is enabled by working Examples 7-11.

Example 9 shows that disorazole D1 and E1 inhibit β-tubulin polymerization at low concentrations. (Example 9, Table 3, page 18 of the specification). Upon reading example 9, a person of ordinary skill in the art would know one mechanism by which the instantly claimed compounds (as exemplified by disorazoles D1 and E1) inhibit cell proliferation is via inhibition of tubulin polymerization.

Example 10 describes a study in which KB/Hela cells were exposed to different concentrations of disorazole E1, paclitaxel or vindesine for 24 hours at 37°C. The concentrations of disorazole E1, paclitaxel and vindesine that cause 50% of KB/Hela cells to be arrested in the G2/M phase of their cell cycles were determined and listed in Table 4. The results show that disorazole E1 has the highest activity in comparison to paclitaxel and vindesine in inhibiting the KB/Hela cells in the G2/M phase of the cell cycle.

Examples 7 and 8 also enable the scope of claim 4. Example 7 describes antiproliferative action of disorazole E1, D1 as well as that of vindesine and paclitaxel on various tumor cell lines

(KB/Hela, SKOV3, SF-268, NCI-H460 and RKOP 27). The results of this study show that disorazole D1 and E1 are not only more potent, but also highly effective at inhibiting proliferation of the studied tumor cells lines than either vindesine or paclitaxel. (Specification, Example 7, page 16). Example 8 describes antiproliferative action on multi-drug resistant and non-resistant tumor cell lines: Acute myeloid leukemia cell line LT12 and resistant line LT12/mdr as well as murine P388 cell line and doxorubicin-resistant P388 (LT12, LT12mdr, P388 and P388ADR). The results of this study show that disorazole E1 not only exhibits potent inhibitory action on all tumor cell lines tested, but also shows superior potency than either of paclitaxel or vindesine. (Specification, Example 8, Table 1, page 17). Therefore, a person of ordinary skill in the art, upon reading examples 7 and 8, would be reasonably enabled to use the instantly claimed compounds (exemplified by disorazole D1 and E1) for the treatment of a disease in humans or animals which is based on the rapid and uncontrolled proliferation of endogenous cells with reasonable expectation of success.

Moreover, a correlation exists between in vitro and in vitro activities of disorazole E1. Example 11 describes such in vivo and in vitro correlation of activities. In this example, disorazole E1 is administered intravenously to NCI-H460 tumor xenograft-bearing nude mice. The results of this experiment show that disorazole E1 produced significant reduction in the tumor growth even at doses that produced no significant weight decrease or mortality in the studied mice. (Specification, Example 11, pages 21-22). These results bolster the validity of the reasonable expectation of success of treatment of a disease in humans or animals which is based on the rapid and uncontrolled proliferation of endogenous cells.

One of ordinary skill in the medical arts, upon reading Examples 7-11, would be enabled not only to use compounds of the invention to treat oncoses, but also would be expected to have reasonable expectation of success of such treatment.

Based on the foregoing, Applicant respectfully requests reconsideration of claim 4 and withdrawal of the rejection thereof.

Claim 5 is directed to a method for the treatment of a disease in humans or animals which is based on the rapid and uncontrolled proliferation of endogenous cells comprising administering the compound of *formula Ia* to a human or animal in need of such treatment.

Examples 7 and 8, among others, enable the scope of claim 3. Example 7 describes antiproliferative action of disorazole E1, D1 as well as that of vindesine and paclitaxel on various tumor cell lines (KB/Hela, SKOV3, SF-268, NCI-H460 and RKOP 27). The results of this study show that disorazole D1 and E1 are not only more potent, but also highly effective at inhibiting proliferation of the studied tumor cells lines than either vindesine or paclitaxel. (Specification, Example 7, page 16). Example 8 describes antiproliferative action on multi-drug resistant and non-resistant tumor cell lines: Acute myeloid leukemia cell line LT12 and resistant line LT12/mdr as well as murine P388 cell line and doxorubicin-resistant P388 (LT12, LT12mdr, P388 and P388ADR). The results of this study show that disorazole E1 not only exhibits potent inhibitory action on all tumor cell lines tested, but also shows superior potency than either of paclitaxel or vindesine. (Specification, Example 8, Table 1, page 17). Therefore, a person of ordinary skill in the art, upon reading examples 7 and 8, would be reasonably enabled to use the instantly claimed compounds (exemplified by disorazole D1 and E1) for the treatment of a disease in humans or animals which is based on the rapid and uncontrolled proliferation of endogenous cells with reasonable expectation of success.

A correlation exists between in vitro and in vitro activities of disorazole E1. Example 11 describes such in vivo and in vitro correlation of activities. In this example, disorazole E1 is administered intravenously to NCI-H460 tumor xenograft-bearing nude mice. The results of this experiment show that disorazole E1 produced significant reduction in the tumor growth even at doses that produced no significant weight decrease or mortality in the studied mice. (Specification, Example 11, pages 21-22). These results bolster the validity of the reasonable expectation of success of treatment of a disease in humans or animals which is based on the rapid and uncontrolled proliferation of endogenous cells. Example 11 clearly shows that the examples in this specification are working examples and therefore enable a person of ordinary skill to practice the method of claim 5 as recited. Therefore, Applicant request reconsideration of claim 5 and withdrawal of the rejection thereof.

Claims 6-8 have been cancelled and so their rejection is moot.

Claim 9 is directed to a method for the treatment of benign or malignant oncoses in humans or animals comprising administering the compound of *formula Ia* to a human or animal

in need of such treatment. As argued in claims 4-5, Examples 7-11 enable the scope of claim 9. Example 7 shows that antiproliferative action of disorazole E1, D1 on various tumor cell lines (KB/Hela, SKOV3, SF-268, NCI-H460 and RKOP 27) far exceeds that of vindesine and paclitaxel. Example 8 shows that disorazole of the invention exhibit antiproliferative action even on multi-drug resistant: Acute myeloid leukemia cell line LT12 and resistant line LT12/mdr as well as murine P388 cell line and doxorubicin-resistant P388 (LT12, LT12mdr, P388 and P388ADR). Example 9 shows that disorazole D1 and E1 inhibit β-tubulin polymerization at low concentrations. All these results show that compounds of the invention are effective against various oncoses and therefore enable one of ordinary skill in the art to use compounds of *formula Ia* to treat these oncoses with reasonable expectation of success.

Claims 10-12 depend from claim 9 and as such the are enabled by the examples of the specification as argued above for claim 9. Claim 13 depends from claim 12, which as already stated depends from claim 9.

Claim 14 is a pharmaceutical composition that depends from claim 3. Rejection of claim 14 under 35 U.S.C 112, First Paragraph for not being reasonably enabled by the specification for treating oncoses, uncontrolled proliferation, infective diseases or immunomodulatory action is absurd. Claim 14 is not a method of use claim and as such the reason its rejection based on the stated reason improper. Therefore, Applicant respectfully requests reconsideration of claim 14 and withdrawal of the improper rejection under 35 U.S.C 112, First Paragraph.

35 U.S.C. 102(b) : First Rejection

Claims 1-4 are rejected under 35 U.S.C.102(b) as being anticipated by Jansen et. al. (Liebig Ann. Chem. **1994**, 759-773) ("Jansen et. al."). In particular disorazole E1-E3, respectively compounds **19-21** on page 765 of Jansen et. al., are cited as being the same as instantly claimed compounds.

Claim 1 has been amended to exclude disorazole E1-E3 (compounds **19-20**) and disorazole F2, which is described as compound **23** on page 767 of Jansen et. al. Since claim 2 depends from claim 1 it also excludes disorazole E1-E3 (compounds **19-20**, page 765 of Jansen

et. al.) and disorazole F2 (compound 23, page 767 of Jansen et. al.). Therefore, claims 1-2 are free of prior art compounds. Since compounds of claims 1-2 are novel over Jansen et. al., Applicant respectfully requests reconsideration of these claims and withdrawal of the rejection.

Claim 3 is directed to a pharmaceutical composition comprising a disorazole compound represented by generic formula Ia. Please see claim 3 for more details of the scope of the generic for formula Ia. No record of said pharmaceutical composition exists in Jansen et. al. Therefore, the pharmaceutical composition of claim 3 is novel and patentable over Jansen et. al. In light of the foregoing Applicant respectfully requests reconsideration of claim 3 and withdrawal of the rejection.

Claim 4 is directed to a method for the treatment of oncoses comprising administering the compound of *formula Ia* to an individual in need of such treatment alone or in combination with a cytotoxic substance and/or an inhibitor of signal transduction. The use of the disorazole compound of *formula Ia* to treat tumoral diseases is not described in Jansen et. al. Therefore, Jansen et. al. do not anticipate claim 4. Hence, claim 4 is novel and patentable over Jansen et. al. In light of the foregoing Applicant respectfully requests reconsideration of claim 4 and withdrawal of the rejection under 35 *U.S.C* 102(b).

35 U.S.C. 102(b) : Second Rejection

Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by H. Irschik et. al. (J Antibiot (Tokyo). **1995** Jan; 48(1):31-5) ("Irschik et. al."). In particular disorazole A1 (Fig. 1 and Table 1) on page 31 of Irschik et. al., is cited as being the same as instantly claimed compounds.

Irschik et. al. do not anticipate claims 1-2. The reason for this is that disorazole A1, disorazole E1-E3 and disorazole F2 are all excluded from claim 1. Since claim 2 depends from claim 1 it is also free of disorazole A1. Therefore, claims 1-2 are novel and patentable over Irschik et. al. Since claims 1-2 are novel and patentable over Irschik et. al., Applicant respectfully requests reconsideration of these claims and withdrawal of the rejection.

Claim 3 is directed to a pharmaceutical composition comprising a disorazole compound represented by generic formula Ia. Please see claim 3 for more details of the scope of the generic *formula Ia*. Note that claim 3 explicitly disclaims disorazole A1. The following is a quotation of the disclaimer.

> "....with the proviso that the compound [according to formula Ia] in which R1 is methoxy, R2, R3 are hydrogen, X is oxygen and Y is the part of a double bond is excluded..." (claim 3)

Since claim 3 does not even recite a pharmaceutical composition of disorazole A1, Irschik et. al. is irrelevant as prior art. Therefore, Applicant respectfully requests reconsideration of claim 3 and withdrawal of the rejection of claim 3 on the basis of Irschik et. al.

Claim 4 is directed to a method for the treatment of oncoses comprising administering the compound of the generic *formula Ia* to an individual in need of such treatment alone or in combination with a cytotoxic substance and/or an inhibitor of signal transduction. The use of a disorazole compound of *formula Ia* to treat tumoral diseases is not described in Irschik et. al. Moreover, disorazole A1 is explicitly disclaimed in claim 4. For these reasons Irschik et. al. is irrelevant as prior art with respect to claim 4. Therefore, Applicant respectfully requests reconsideration of claim 3 and withdrawal of the rejection.

The Commissioner is authorized to charge any required fees, including any extension and/or excess claim fees, any additional fees, or credit any overpayment, to Goodwin Procter LLP Deposit Account No. 06-0923.

Respectfully submitted for Applicant,

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